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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/593,538	09/19/2006	Ippei Sakimoto	06659/LH	9964

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FRISHAUF, HOLTZ, GOODMAN & CHICK, PC
220 Fifth Avenue
16TH Floor
NEW YORK, NY 10001-7708

EXAMINER	
GOON, SCARLETT Y	

ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,538	SAKIMOTO ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *21 July 2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the Applicants' Remarks filed on 15 August 2008.

Claims 9-16 are currently pending.

The declaration of Dr. Keisuke Ohta (inventor), submitted by Applicants on 15 August 2008 under 37 CFR § 1.132, are acknowledged and will be further discussed below.

Information Disclosure Statement

The information disclosure statement (IDS) dated 21 July 2008 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of squamous carcinoma, does not reasonably provide enablement for the treatment of other types of cancers. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to use the invention commensurate in scope with these claims.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

All of the *Wands* factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The rejected invention is drawn towards the method for treating cancers by administering to a subject in need thereof an effect amount of a radiosensitizer in combination with radiation.

Breadth of claims: The claims are extremely broad in that they encompass literally the treatment of all types of cancers.

Amount of guidance/Existence of working examples: Working examples are present which show that the compounds claimed are effective against squamous carcinoma cells. However, there is no guidance in the specification, nor are there any working examples, to show that the claimed compounds are effective against other types of cancers, such as adenocarcinoma cancer.

State of the prior art/Predictability or unpredictability of the art: The prior art teaches that the claimed compounds are useful as an anticancer agent (US Patent No. 6,518,410 B2). These compounds are effective in the treatment of colon cancer, lung cancer and gastric cancer (US Patent No. 6,518,410 B2). However, there is no prior art which teaches that the claimed compounds can treat other classes of cancer. Moreover, Park *et al.* teaches that radiotherapy is only effective in treating only specific kinds of cancers such as lung cancer, mammary cancer, and uterine cancer, while some other kinds of cancers show only partial effects or develop resistance to radiotherapy (PTO-892, ref. C, paragraph 0004)

Therefore, in view of the *Wands* factors as discussed above, there is no clear and convincing evidence in sufficient support of the use of the claimed compounds for the treatment of all types of cancers.

Response to Arguments

Applicant's arguments filed 15 August 2008 with respect to the rejection of claims 9-16 made under 35 USC § 112, first paragraph, for lack of enablement for the treatment of all cancer types other than squamous carcinoma, and the Declaration of Dr. Ohta submitted on 15 August 2008, have been fully considered but they are not persuasive.

Applicants argue that in Experimental Example 1-6, uterine cervical cancer (HeLa cells) are derived from adenocarcinoma and in Experimental Example 1-7, lung cancer (A549 cells) are derived from adenocarcinoma. Applicants further provided a

Declaration under 35 USC § 1.132 indicating that other types of cancers, i.e. prostate adenocarcinoma in Experiment 1 and colorectal adenocarcinoma in Experiment 2, can also be treated with the present invention, and also provided details for the origin of the various cell lines used in their experiments. This argument is ineffective to overcome the 35 USC § 112 rejections made under the first paragraph because, while Applicants have sufficiently shown that the invention can be used to treat various types of squamous carcinoma and adenocarcinoma, there is still no evidence that the combined treatment can be used to treat all other types of cancer, as instantly claimed. The instant claims are drawn to a treatment for the broad class of cancers. However, squamous carcinoma and adenocarcinoma represent only two sub-types of cancer. For example, there is no evidence that the combined treatment can be used for the treatment of leukemia.

Therefore, the declaration of Dr. Ohta is insufficient to rebut the lack of enablement case herein.

The rejection is still deemed proper and therefore adhered to.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,518,410 B2 to Yamazaki *et al.* (herein referred to as the '410 patent), published US patent application no. 2004/0181114 A1 by Hainfeld *et al.*, and published US patent application no. 2003/0166692 A1 by Park *et al.*

The '410 patent discloses sulfoquinovosylacylglycerol derivatives that may be used as an immunosuppressive agent, anticancer agent, and DNA polymerase α inhibitor (abstract; column 2, lines 35-42). These compounds exhibit low toxicity and usability of long-term administration (column 2, lines 38-39). The sulfoquinovosylacylglycerol derivatives disclosed in the '410 patent have the structure as shown in formula (1-1). In formula (1-1), R_{101} represents an acyl residue of a higher fatty acid, wherein the acyl residues include groups represented by R-C(=O), where R represents an alkyl or alkenyl group having 13 or more carbon atoms, preferably in the range of 13 or more and 25 or less (column 4, lines 21-34; claim 1). Additionally, the acyl group of R_{101} can be represented by the formula $CH_3(CH_2)_nCO$-, wherein n is an integer from 12-24, or having only an even number between 12-24 (claims 4, 21-22 and 24). This results in R_{101} having an acyl chain which contains an odd number of carbons, from 13-25. In formula (1-1), R_{102} represents a hydrogen atom or an acyl residue with the same independent meaning as those of the R_{101} group (column 4, lines 44-47; claim 1). The inhibitory activity of the various sulfoquinovosylacylglycerol derivatives are shown in table 7 (columns 37-38). The anti-cancer activity of various sulfoquinovosylacylglycerol derivatives against colon cancer cells and gastric cancer cells is shown in tables 8 and 9, respectively (columns 39-40). The '410 patent does

not teach the method wherein the compounds are used in combination with irradiation to treat cancers.

Hainfeld *et al.* teaches methods for enhancing radiation effects with metal nanoparticles. Radiation has commonly been used as a method of treating cancers. However, a drawback to the treatment of cancers by radiation alone is that radiations are not generally very specific for the tumor (paragraph 0002). An alternative is the use of compounds that act in combination with radiation to produce an improved response, usually by making DNA more susceptible to radiation (paragraph 0003). These compounds are generally known as radiosensitizers. Some radiosensitizers are themselves anti-cancer chemotherapeutic drugs that appear to work synergistically with x-irradiation (paragraph 0004). Instead of compounds as radiosensitizers to enhance radiation, another type of radiation enchancement method uses a metal surface, known as photoactivation. Hainfeld *et al.* provides methods of using metal nanoparticles to enhance the dose and effectiveness of x-rays or other kinds of radiation in therapeutic regimes of ablating a target tissue such as tumor (abstract; paragraph 0001).

Park *et al.* teaches a method of administering a composition comprising [N'-(phenyl-pyridin-2-yl-methylene)-hydrazine carbodithioic acid methyl ester] in combination with radiation for enhancing radiotherapy on cancerous cells or tumors (abstract; paragraph 0001; claims 10-11 and 13). Chemotherapy-radiotherapy combinations are administered to treat a variety of cancers, based on the theory that the mechanisms for each method, and their toxicities, do not overlap. The necessary conditions of candidate anticancer drugs that can also be used as radiotherapy-

enhancing agents are 1) they enhance the anticancer effect of radiation therapy, 2) they cause no damage to normal cells, and 3) they have minimal toxicity (paragraph 0009). Park *et al.* indicates that [N'-(phenyl-pyridin-2-yl-methylene)-hydrazine carbodithioic acid methyl ester] is synergistically effective in treating cancerous cells or tumors when used in combination with radiotherapy, compared to irradiation only. Thus, a method for enhancing radiotherapy on cancers in mammals is provided, which comprise administering the effective amount of [N'-(phenyl-pyridin-2-yl-methylene)-hydrazine carbodithioic acid methyl ester] in combination with radiation (paragraph 0023). Preferably, [N'-(phenyl-pyridin-2-yl-methylene)-hydrazine carbodithioic acid methyl ester] is first administered, followed by irradiation.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of the '410 patent, concerning sulfoquinovosylacylglycerol derivatives that may be used as immunosuppressive agents, anticancer agents, and DNA polymerase α inhibitors, with the teachings of Hainfeld *et al.*, regarding methods for enhancing radiation effects with compounds or metal nanoparticles, with the teachings of Park *et al.*, regarding a method for administering a composition comprising [N'-(phenyl-pyridin-2-yl-methylene)-hydrazine carbodithioic acid methyl ester] in combination with radiation for enhancing radiotherapy on cancerous cells or tumors. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Park *et al.*, and exemplified by Hainfeld *et al.*, that a combination treatment of chemotherapy-radiotherapy can mediate anti-cancer effects via different mechanisms. Thus, the said

combination of cancer treatments, e.g. administering a sulfoquinovosylacylglycerol derivative in combination with irradiation, is expected to have synergistic effects on treating cancers since sulfoquinovosylacylglycerol derivatives are known to inhibit DNA polymerase α which controls DNA synthesis, thereby making it more susceptible to radiation. As Hainfeld *et al.* indicated, compounds that make DNA more susceptible to radiation can be used in combination with radiotherapy to enhance the radiation effects.

Absent of any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in treating cancers by combining the use of the anticancer sulfoquinovosylacylglycerol derivatives, as disclosed in the '410, with the radiation therapy methods discussed by Hainfeld *et al.* and Park *et al.*

Response to Arguments

Applicant's arguments filed 15 August 2008 with respect to the rejection of claims 9-16 made under 35 USC § 103(a) as being unpatentable over US Patent No. 6,518,410 B2 to Yamazaki *et al.* (herein referred to as the '410 patent), published US patent application no. 2004/0181114 A1 by Hainfeld *et al.*, and published US patent application no. 2003/0166692 A1 by Park *et al.*, and the Declaration of Dr. Ohta submitted on 15 August 2008, have been fully considered but they are not persuasive, as discussed below.

Applicants argue that the Hainfield *et al.* and Park *et al.* references do not include a "sugar skeleton" or "acyl residue of higher fatty acid" of the compound of formula (1)

as recited in claim 1, and therefore provides no reason that the instantly claimed compounds would have an effect as a radiosensitizer. This argument is not persuasive. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The primary reference, the Yamazaki '410 patent, already discloses the compounds of the instant claims and further indicated that the compounds can be used as an anticancer agent and DNA polymerase α inhibitor, as indicated in the Office Action dated 22 April 2008. Furthermore, as indicated in the previous Office Action, Hainfield *et al.* taught that compounds that make DNA more susceptible to radiation are known as radiosensitizers, and can thus work synergistically with irradiation (paragraphs 0003 and 0004). Park *et al.* taught that radiotherapy can be enhanced when used in combination with an anticancer drug and further showed synergistic effects of chemotherapy-radiotherapy combinations when administered to treat a variety of cancers. Thus, it is the combined teachings of the prior art, as indicated in the previous Office Action, that would motivate one to use the compounds of the present invention, in combination with irradiation, to treat cancer. As indicated in the previous Office Action, and restated in the rejection indicated above, the said combination of cancer treatments, e.g.

administering a sulfoquinovosylacylglycerol derivative in combination with irradiation, is expected to have synergistic effects on treating cancers since sulfoquinovosylacylglycerol derivatives are known to inhibit DNA polymerase α which controls DNA synthesis, thereby making it more susceptible to radiation, according to the combined teachings of the prior art. As Hainfeld *et al.* indicated, compounds that make DNA more susceptible to radiation can work synergistically with irradiation (paragraph 0004).

Applicants further argue that the synergistic effect obtained by the combined treatment of the present invention is totally unexpected based on the prior art. This argument is not persuasive, because as previously indicated in the above response, Hainfeld *et al.* specifically teach that compounds that make DNA more susceptible to radiation can work synergistically with irradiation (paragraph 0004). The Yamazaki '410 patent previously disclosed the instantly claimed compounds can be used as an anticancer agent and DNA polymerase α inhibitor. Thus, the combined teachings of the prior art do suggest a synergistic effect when the compounds disclosed in the Yamazaki '410 patent is used in combination with irradiation.

Applicants further argue that in the present invention, the radiosensitizer exhibits its effect at a low administration concentration, and that the radiosensitizer can be used in combination with a low dose of irradiation. Applicants further provided a Declaration under 35 USC § 1.132 to support their argument that the radiosensitizer has sufficient therapeutic effect even when performed in combination with a low irradiation dose. This

argument is not persuasive because the claims are drawn to a method of treating cancer comprising the composition, with no limitations regarding the concentration of radiosensitizer or dose of irradiation. Furthermore, as it is well-known that chemotherapy and radiotherapy can also destroy normal cells in addition to the cancerous cells, it is considered *prima facie* obvious that one of ordinary skill in the art would optimize the concentrations of radiosensitizer and dose of irradiation when providing treatment, so as to minimize harm caused to the cancer individual.

Therefore, the declaration of Dr. Ohta is not persuasive to rebut the *prima facie* case herein.

Applicants additionally argue that the combined treatment of the present invention exhibits its advantageous effect against various types of cancers while Park *et al.* disclose that their treatment is only applicable to specific kinds of cancers, and thus the effectiveness of the present invention against various types of cancers cannot be expected by a person skilled in the art. This argument is not persuasive because, as indicated in the "Response to Arguments" of the rejections made under 35 USC § 112, first paragraph, Applicants have not sufficiently shown that their method of treatment is applicable to <u>all</u> types of cancers. Furthermore, Park *et al.* teach that their method of chemotherapy-radiotherapy treatment is applicable to a broad range of cancers, including primary and metastatic cancers that include gastric cancer, lung cancer, ovarian cancer, prostate cancer, liver cancer, uterine cancer, thyroid cancer, pancreatic cancer, lingual cancer, bile duct cancer, rectal cancer, mammary cancer, and skin

cancer [paragraph 0037]. These cancer sub-types are similar to those taught in the Applicants' instant Specification.

The rejection is still deemed proper and therefore adhered to.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623

/SCARLETT GOON/
Examiner
Art Unit 1623